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CT imaging for evaluation of calcium crystal deposition in the knee: initial experience from the Multicenter Osteoarthritis (MOST) study

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SUMMARY

Objective: Role of intra-articular calcium crystals in osteoarthritis (OA) is unclear. Imaging modalities used to date for its evaluation have limitations in their ability to fully characterize intra-articular crystal deposition. Since Computed Tomography (CT) imaging provides excellent visualization of bones and calcified tissue, in this pilot project we evaluated the utility of CT scan in describing intra-articular calcium crystal deposition in the knees.

Method: We included 12 subjects with and four subjects without radiographic chondrocalcinosis in the most recent visit from the Multicenter Osteoarthritis (MOST) study, which is a longitudinal cohort of community-dwelling older adults with or at risk for knee OA. All subjects underwent CT scans of bilateral knees. Each knee was divided into 25 subregions and each subregion was read for presence of calcium crystals by a musculoskeletal radiologist. To assess reliability, readings were repeated 4 weeks later.

Results: CT images permitted visualization of 25 subregions with calcification within and around the tibio-femoral and patello-femoral joints in all 24 knees with radiographic chondrocalcinosis. Intra-articular calcification was seen universally including meniscal cartilage (most common site involved in 21/24 knees), hyaline cartilage, cruciate ligaments, medial collateral ligament and joint capsule. Readings showed good agreement for specific tissues involved with calcium deposition (kappa: 0.70, 95% CI 0.62–0.80).

Conclusion: We found CT scan to be a useful and reliable tool for describing calcium crystal deposition in the knee and therefore potentially for studying role of calcium crystals in OA. We also confirmed that "chondrocalcinosis" is a misnomer because calcification is present ubiquitously.

Introduction

Despite knee osteoarthritis (OA) being the most common form of joint disease affecting older adults and a leading cause of lower-extremity disability globally[1,2], no effective disease-modifying pharmacologic therapies are available at this time. This reflects, in part, an incomplete understanding of the underlying pathogenesis of OA. A relatively understudied potential contributor to the disease pathogenesis is intra-articular calcium crystals, which often co-exists with knee OA although their exact role is unclear[3]. There are two main types of calcium crystals i.e., calcium pyrophosphate (CPP) and basic calcium apatite (BCP) crystals, which differ in chemical properties, appearance and presentation and potentially in their role in OA[4,5]. While one school of thought considers these crystals as "innocent bystanders" or the natural consequence of the joint damage[6], others posit that these crystals play an active role in cartilage destruction by induction of "oxidative stress" through release of inflammatory cytokines and matrix metalloproteases[7]. If calcium crystals do in fact contribute to cartilage degeneration in OA, then it would cast them as a novel target for the treatment and prevention of OA.

A major challenge in assessing the role of calcium crystals in OA to date has been the practical imaging modality that provides

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accurate visualization of intra-articular calcium crystals. Conventional radiography is the most commonly used imaging method for visualization of intra-articular calcium. However, its use is limited because of its poor sensitivity, limiting insights into burden and localization[8]. While ultrasonography has been found to be a sensitive tool in identifying cartilage calcification[9], its inability to visualize tissues deep to bone surfaces, and thus inability to visualize some cartilage and soft tissue surfaces (including the cruciate ligaments) is a limitation[10,11]. There are also questions about specificity of ultrasound for CPP crystals[8]. Traditional MRI pulse sequences are also limited in sensitivity and in their ability to distinctly identify calcified cartilage from other abnormalities, such as meniscal tears[12,13] which may be overcome by using ultrashort-echo-time MR sequence, as shown in a feasibility study[14]. To that end, computed tomography (CT) is of interest because it provides highly spatial, 3-dimensional information to identify presence of pathologic processes within scanned anatomical regions with excellent visualization of bones and calcified tissues, yet it has not been studied extensively for calcium crystal deposition.[15,16]

As the burden of OA is rising, the need for understanding the role of depositions of calcium crystals as part of a larger effort to understand underlying pathophysiology of OA is becoming crucial. We therefore undertook this pilot project to examine the utility of CT scans in describing intra-articular calcium crystal deposition, particularly in evaluating the precise tissues involved, among subjects with and without radiographic presence of calcium crystals (chondrocalcinosis).

Methods

Study sample

All participants in this study were recruited from the Multicenter Osteoarthritis (MOST) Study, a NIH-funded multicenter, longitudinal, observational study of 3026 individuals at baseline, who had or were at high risk for knee OA, recruited from two US centers, Iowa City Iowa and Birmingham, Alabama. Details of the study population have been published elsewhere[17]. All participants in the MOST Study had fixed-flexion bilateral knee x-rays at baseline and at each follow-up study visit (30-, 60- and 84-month visits).

We included 16 subjects from the Iowa study site who had X-rays obtained at the 84-month (most recent) follow-up visit (5/5/11–12/17/12), 12 subjects read by the MOST X-ray readers as having chondrocalcinosis in both knees and four with no evidence of chondrocalcinosis in either knee.

Because cartilage loss and consequent joint space narrowing can compromise assessment of intra-articular calcification, we preferentially selected subjects who did not have radiographic OA (Kellgren and Lawrence grade <2)[18] to ensure that the joint space was preserved to optimize visualization of calcium deposition of intra-articular tissues. In fact, in a recent study evaluating sensitivity and specificity of CT scans for diagnosing gout, all false positives had advanced OA[19]. In our study, out of 32 knees, six had definite radiographic OA (KL grade ≥2) and none had a KL grade of 4.

CT scanning

An advance to conventional CT, Dual Energy CT (DECT) was obtained given its availability at the research facility (Department of Radiology, University of Iowa, Iowa city, Iowa) and plans for a future study of comparison of intra-articular calcium crystal vs urate crystal deposition. All 16 participants underwent CT scanning using a Definition Flash scanner Siemens Healthcare of bilateral knees. For this study, we utilized only the images from one of the two X-ray guns in the DECT acquisition mode. The scan protocol from the X-ray gun selected used an effective mAs of 45, kV of 140, 0.8 pitch and a rotation speed of 0.285 s. The raw projection data were reconstructed using a slice thickness of 0.6 mm and a slice interval of 0.3 mm with a standard 512 × 512 imaging matirx. Reconstruction diameters (DFOV) were standardized to approximately 15 cm for each respective knee data set. The DFOV provided a in-plane resolution 0.3 mm (× plane) × 0.3 mm (y plane) which corresponded to an isotrophic voxel dimension of 0.3 mm × 0.3 mm × 0.3 mm when using a slice interval of 0.3 mm in the z-plane. A high spatial reconstruction kernel of B70 was used to increase the CNR of the anatomical structures. The radiation dose for knee joint for DECT is the same as single energy CT scans, which is 0.15 mSv for one knee[20], compared to 0.001–0.005 mSv for knee X-ray, but less than the average annual natural background radiation dose (2.4 mSv).[21]

A two-step scoring system was devised. First, each knee was divided into 25 subregions. Then, each subregion within a knee was read by a board certified musculoskeletal radiologist with 15 years of experience in semi-quantitative scoring of knee OA features (AG) for presence (yes/no) of calcium crystals separately. The location of the calcium deposition and the shape of the structure in which calcium was deposited made it possible to identify the tissue affected. Readings were repeated after 4 weeks for calculation of intra-rater reliability. We used the axial images but also the coronal and sagittal reformatted images when semi-quantitatively scoring the knees. We performed multiplanar reformats (MPR) in sagittal and coronal planes and smooth reconstruction kernels in order to reduce the image noise. We also created maximum-intensity projection (MIP) images.

Statistical analysis

The intra-rater reliability for presence (yes/no) of intra-articular calcium crystals overall and in specific subregions (hyaline cartilage and meniscal cartilage) between readings 1 and 2 was measured by calculating kappa statistics (95% confidence interval) using SAS 9.3 (SAS Inc., NC).

This study was approved by Institutional Review Board as well as the Radiation Safety committee at University of Iowa, Iowa city, Iowa where subjects were scanned.

Results

In comparison with the participants without radiographic chondrocalcinosis ($n = 4$), those with radiographic chondrocalcinosis ($n = 12$) in this study were older (mean age 72 vs 64 years) and had lower mean BMI (26 kg/m^2 vs 32 kg/m^2). Seven out of 12 subjects and three out of four subjects were women in the chondrocalcinosis and non-chondrocalcinosis, respectively. While female predominace has been noted in prior studies of chondrocalcinosis[22], in our study that is not the case likely due to small number of total participants. A history of knee injury was present among two subjects with radiographic chondrocalcinosis.

Intra-articular calcium crystals were detected on CT images of all 24 knees (12 subjects) with bilateral radiographic chondrocalcinosis and not detected in any of the eight knees (four subjects) without radiographic chondrocalcinosis. CT images provided excellent visualization of intra-articular tissue structures and calcium crystal deposition was noted not only in meniscal and hyaline cartilage but also in deeper structures including cruciate ligaments and joint capsules. In Fig. 1, 3-D CT images of knee joint with and without intra-articular calcium deposition is shown. Fig. 2 demonstrates calcium crystal deposition in femoral hyaline cartilage, meniscal cartilage and joint capsule in a subject with

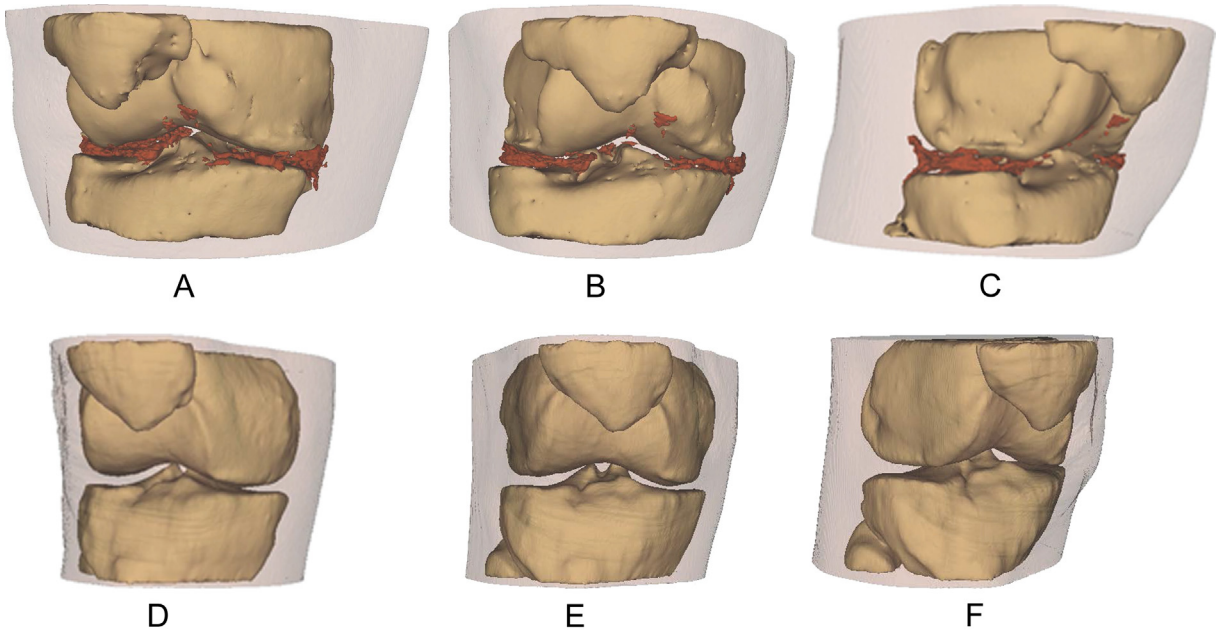

Fig. 1. [A-C] 3-D CT images of the knee of a subject with chondrocalcinosis show meniscal and chondral calcifications.[D-F] 3-D CT images of the knee of a subject without chondrocalcinosis show no calcification at the tibio-femoral joint.

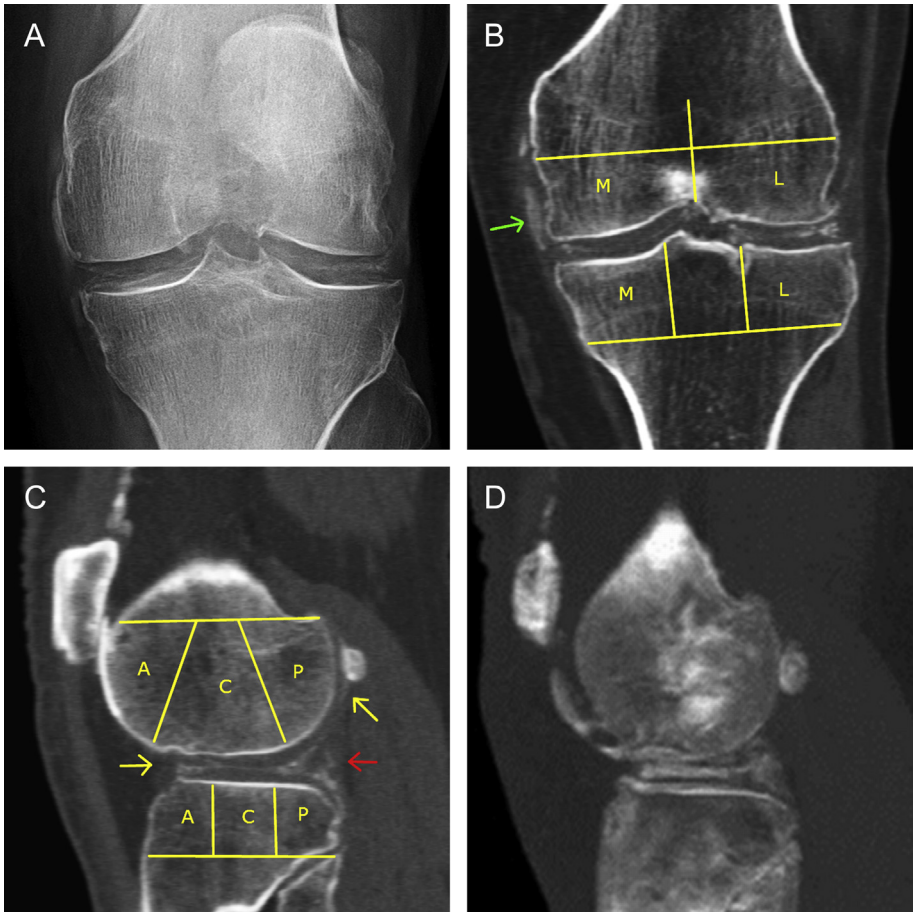

Fig. 2. X-ray depicting chondrocalcinosis in the knee as medial and lateral meniscal calcifications (A). Coronal (B) and sagittal (C) CT image reformats of the same knee (with segmentation) demonstrating distribution of calcium crystals in the menisci and cartilage. Note the PA X-ray and coronal CT reformat (although a slice) show similar depositions except for deposition in medial capsule and collateral ligament (green arrow). The sagittal CT reformat (C) and MIP (D) provide a more comprehensive picture of deposition location. Arrows show meniscal deposition (red arrow) and hyaline cartilage deposition (yellow arrow) but also in the supra patellar articular capsule.

radiographic chondrocalcinosis. Additional images demonstrating distribution of calcium crystals in cartilage, ligaments and joint capsule are presented in a video as supplementary data.

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.joca.2014.10.009.

Menisci were the most commonly involved structures however, hyaline cartilage, cruciate ligaments and joint capsule were also frequently involved (Table I). The intra-rater reliability for overall presence of intra-articular calcium crystals in specific subregions between readings 1 and 2 was excellent (kappa: 0.70, 95% CI 0.62-0.80).

Discussion

In this study, we found that CT scan can provide comprehensive assessment of intra-articular calcium crystal deposition owing to its MPR ability[23]. While there was no discrepancy between X-ray and CT scan in terms of detection of calcification, due to 3-D images, CT enabled detection of calcium crystals in deeper intra-articular structures such as cruciate ligaments and joint capsule which was otherwise not possible by conventional radiography. Further, our study demonstrated excellent intra-rater reliability for detection of calcium crystal deposition at specific subregions within the knee joint.

Table I
Intra-articular calcium crystal deposition involving specific subregions on CT images among knees with radiographic chondrocalcinosis ($N = 24$)

Tissue subregions	Number of knees with presence of calcification at each specific soft tissue site	
	Reading 1	Reading 2
Femur Hyaline Cartilage		
Medial		
Anterior	12	14
Central	14	12
Posterior	22	22
Lateral		
Anterior	8	10
Central	16	14
Posterior	13	13
Tibia Hyaline Cartilage		
Medial		
Anterior	3	2
Central	6	6
Posterior	8	5
Lateral		
Anterior	8	4
Central	12	7
Posterior	13	13
Patellar Hyaline Cartilage		
Medial	12	11
Lateral	9	11
Meniscus Fibrocartilage		
Medial		
Anterior	16	17
Body	20	23
Posterior	22	23
Lateral		
Anterior	21	22
Body	22	23
Posterior	22	22
Ligaments		
ACL	10	10
PCL	13	19
MCL	3	3
LCL	0	0
Capsule	15	14

Our findings have implications. Firstly, our study provides new insight with respect to calcium crystal deposition in subjects with radiographic chondrocalcinosis. We found that in subjects with radiographic chondrocalcinosis, calcification is not limited to cartilage, but rather ubiquitously present, involving ligaments and joint capsules. In that sense, our findings confirm that the term chondrocalcinosis, which refers to cartilage calcification on radiographs, is a misnomer. Secondly, our CT imaging can potentially be used to detect intra-articular calcium crystal deposition in early stages. This is possible in two scenarios: (1) calcification may be present in other intra-articular structures without yet involvement of cartilage; or (2) calcification may have local effects on cartilage without being deposited in sufficient quantity to be detected by plain radiography; and (3) presence of less prolific deposition of calcium crystals on X-ray may appear as osteophytes. Thus, CT may be the ideal imaging method to study role of calcium crystals in OA pathogenesis.

Further, our study extends observations from a recent study using CT imaging for detection of calcium crystal deposition in the knee and its correlation with knee OA in 68 non-embalmed cadaveric knees (mean age 84 years)[24]. Calcification in meniscus (34% knees) and hyaline cartilage (21% knees) were noted to be common and significantly correlated[24]. Since these knees were not selected in advance to have chondrocalcinosis, the extent of calcium deposition was less than our study knees. Unlike our study, calcification of other intra-articular structures was not reported in that study.

While we found advantages of CT scan in describing calcium crystals in and around the joints, we also acknowledge some limitations. One limitation of conventional CT scan is that it may not be able to distinguish between the different types of calcium crystals. Second, when using ionizing radiation such as in CT, there is concern for radiation exposure. However, as demonstrated by Biswas *et al.*, radiation exposure in the knee area is not as much of a concern[20]. Sticking with the ALARA principle (As Low As Reasonably Achievable), there are radiation reduction techniques, mainly used for more radiation sensitive areas, are available options in the OA knee protocols as well. Since bone marrow in the knee is not weighted as sensitive as main tissue organs of the body, longitudinal scanning to follow progression of disease can be achieved well below the natural background levels, even considered within the range of standard X-ray. This allows CT to be a safe and powerful modality with the ability to provide comprehensive detection intra-articular calcium crystal deposition. New advances in CT such as automatic exposure control and Iterative reconstruction, have been shown to reduce CT radiation exposure significantly[25]. Typically, radiation dose studies like the one by Shin at el. are more focused on organs, i.e., cells with a greater likely hood of cancer development such as breast, orbits, and genital tissues[25]. Another study of interest, by Becce at el, compared the use of standard dose using filtered back projection reconstruction, vs a lower dose interative reconstruction method in 40 patient's having cervical spine CT's[26]. Their findings, similar to Shin, demonstrated a 40% lower exposure savings when using an iterative reconstruction technique over conventional filtered back projection.[26]

Few limitations of this study need to be acknowledged. First, because this small pilot project is an initial effort to evaluate utility of CT scans in characterizing calcium crystal deposition, images were read by a single radiology reader. Thus, while we have demonstrated very good intra-rater reliability, having one more reader would have improved reliability by providing inter-rater reliability. Secondly, we were unable to quantitate the burden of calcium crystals in the knee because given prolific deposition involving multiple tissue structures within the joint, accurate assessment of the volume was difficult with the semiquantitative method used to read the CT scans.

In conclusion, despite the small numbers and other limitations as mentioned above, this pilot study provides valuable insight into

potential utility of CT imaging in evaluation of intra-articular calcium crystal deposition and potentially studying role of calcium crystals in OA pathogenesis. Larger studies are needed to confirm our findings, test reliability of the scoring system as well as determine whether quantification of the burden of calcium crystals within the joints is possible using CT scans. Further, advances in CT such as DECT should be evaluated to distinguish different types of calcium crystals in the knee joint, which is not possible by conventional CT scans.

Author contributions

All authors included on the paper as coauthors fulfil the criteria of authorship.

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Competing interests

AG is shareholder of Boston Imaging Core Lab, LLC and Consultant to TissueGene, MerckSerono and Sanofi-Aventis. Others have no conflict of interest.

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